

EDITORIAL COMMENT

Developing Imaging Biomarkers for Myocardial Involvement in Amyloidosis

Challenge and Opportunity*



James E. Udelson, MD

With the increasing recognition of the heterogeneity of patients who have heart failure with preserved ejection fraction (HFpEF), assessing the underlying etiology has assumed substantial clinical importance. Large, randomized trials using broad treatment paradigms for HFpEF patients, such as those examining the role of aldosterone antagonists (1), have not proven positive, suggesting that a therapeutic approach needs to be more targeted. Thus, diagnostic strategies that may uncover a more directly treatable condition are of great interest.

One underlying etiology that presents as the HFpEF syndrome is cardiac amyloidosis. The current understanding holds that cardiac amyloidosis is usually the expression of 1 of 3 diseases associated with the deposition of amyloid-type fibrils in the myocardium (2). Cardiac amyloid may be associated with expansion of a plasma cell clone resulting in deposition of immunoglobulin light chains in the myocardium, known as AL amyloid. Cardiac amyloid may also be the result of deposition of misfolded transthyretin (TTR), a transport protein synthesized by the liver. The TTR syndrome is divided into 2 categories: hereditary, or associated with misfolding of wild-type TTR (2). The latter appears to mostly be clinically manifest in older men. Recent evidence indicates that these 3 major types of cardiac amyloidosis may have distinct phenotypic and prognostic profiles (2).

Treatment of AL amyloid is directed at the expanded plasma cell clone. However, there are also

now potential treatments on the horizon for TTR amyloid, currently being tested in trials (3,4). Hence, identification of the presence of cardiac amyloid and its specific etiology is assuming increasing importance.

The gold standard for diagnosis and assessment of specific amyloid subtype is obtaining tissue using endomyocardial biopsy. However, the expertise needed for this technique limits it to centers specializing in advanced heart failure. Thus, a non-invasive imaging marker that can assist in selecting patients most likely to have a high yield of biopsy, or alternatively rule out the diagnosis with a strong degree of confidence, would be of clinical importance.

SEE PAGE 50

In this issue of *iJACC*, Lee et al. (5) report on a positron emission tomography (PET) tracer known as ¹¹C-Pittsburgh B (PiB) for detection of cardiac amyloidosis, in what is labeled as a pilot study. There are several reports of the use of this agent for imaging amyloid fibrils in the brains of patients with Alzheimer's disease (6). Its affinity for amyloid fibrils is apparently related to the fact that it is derivative of thioflavin-T, a fluorescent dye used in the identification of amyloid fibrils in various organs (7). An initial report described cardiac uptake of ¹¹C-PiB in a small number of patients who had either AL or TTR cardiac amyloidosis (8).

In this report, the investigators studied 22 patients who had evidence of a monoclonal gammopathy and also had a suggestion of cardiac involvement by echocardiography or electrocardiography, or who had biopsy-proven amyloid of a noncardiac organ. The patients underwent PET/computed tomography (CT) imaging to assess the presence and magnitude of ¹¹C-PiB uptake. Most also had endomyocardial biopsy, echocardiography, and cardiac magnetic resonance imaging (CMR). Ten referent control subjects who were sex-matched but not well matched for age were

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the Division of Cardiology and the CardioVascular Center, Tufts Medical Center, Boston, Massachusetts. Dr. Udelson has reported that he has no relationships relevant to the contents of this paper to disclose.

also studied with PET/CT ^{11}C -PiB imaging in an attempt to define a normal range.

Among the 15 patients with biopsy-proven cardiac amyloid (all with the AL type), the ^{11}C -PiB uptake relative to the blood cavity was higher than in those patients with negative biopsies. Figure 1 from the paper (5) suggests that these results were driven by 5 or 6 of the 15 biopsy-positive patients with high values. When using a cut-off value derived from the normal subjects, the point estimate for sensitivity was 87%, with specificity of 100%. Given the modest number of patients, the confidence intervals (CIs) were wide.

The data on this agent are of real interest. Besides the compelling reasons noted earlier to seek out the diagnosis of cardiac amyloid and its specific type, this agent appears to have a mechanism that, in theory, could allow for a better delineation of the magnitude of amyloid deposition within a particular patient than available with prior imaging agents. That would be of potentially great value in clinical trials.

There are some important limitations to the conclusions that can be drawn from this dataset, some of which are acknowledged by the authors. The patients included are limited to those with AL amyloid, although a previous report suggested that ^{11}C -PiB is also taken up in TTR amyloid (8). In such a small dataset, misclassification of disease status by the gold standard test can have a major effect on the results. In the 7 patient biopsy-negative patients, 4 had low voltage on electrocardiogram, and some had unexplained left ventricular hypertrophy, raising the question of sampling error in the biopsies. Finally, typical of many early reports on imaging performance, the focus of the discussion is on the point estimates of the calculated performance characteristics, as the authors refer to the “excellent” sensitivity and specificity of this new agent. However, given the small number of disease positive and disease negative patients, it is more appropriate to examine the CIs, which suggest that the sensitivity and specificity performance of this agent may range from unacceptable (lower CI boundary 58% and 56%, respectively) to almost perfect (upper CI boundary 98% and 100%, respectively). This illustrates why we need to be circumspect about early data such as these, but we must focus on the promise and potential to move forward.

Other radionuclide tracers have been investigated over the years as markers of cardiac amyloid. Beginning more than 30 years ago, various bone-seeking radiotracers have been examined by investigators around the world (9). None has achieved widespread

use, for a variety of reasons. One reason is that the literature on performance characteristics is challenging to synthesize. There are heterogeneities in patient populations as well as in the truth standards used to parse the patients into disease positive and disease negative subsets. Analytic methodologies also vary, with early studies using qualitative assessments, which are of course highly variable, whereas more recent studies incorporate quantitative analytics (9). The present study by Lee et al. (5) illustrates some of these issues. As noted, some of the patients who were disease negative by biopsy had clinical signs suggesting cardiac involvement, such as low voltage on electrocardiography or unexplained hypertrophy on echocardiography. Moreover, even within the biopsy-positive disease subset, some of the patients had been treated for AL amyloid, confounding the assessment of tracer uptake and creating additional small subsets of patients for analysis.

Nonetheless, there are some features of this new agent that are attractive and suggest that further research should be pursued. The apparent mechanism of its uptake and retention may be more specific for the cardiac amyloid infiltrative disease state than prior agents. The use of PET/CT technology brings the promise of more sophisticated analysis of uptake than might be possible with planar or single-photon emission CT imaging of technetium-99m-based tracers.

In the dataset from Lee et al. (5), CMR was also obtained, and the data appeared similar in overall performance, although there was some discordance between the findings of the radionuclide imaging and the CMR results. The small size of the study group here precludes rigorous comparisons. It has been almost 10 years since the initial reports of the use of CMR and gadolinium enhancement imaging in cardiac amyloid (10), documenting the diffuse sub-endocardial uptake pattern. Many reports also involve modest numbers of patients, similar to the radionuclide data. Although the application of CMR techniques with gadolinium are precluded in patients with an important degree of renal dysfunction, the evolving capability of quantitation of myocardial extracellular volume fraction, which may be linked to the magnitude of amyloid deposition, will drive further interest and development.

As previously suggested, the emergence of treatment possibilities for this heretofore progressive syndrome, both for AL amyloid and, more recently, TTR amyloid, makes the development of imaging strategies to screen for the presence of and possibly quantify the magnitude of cardiac involvement a highly compelling and important opportunity for the imaging community. These pilot data on the use of

the ^{11}C -PiB agent represent a small first step in such a direction. Ideally, imaging markers such as this agent would be incorporated into clinical trials of new treatment strategies as a baseline measure, so that analyses could illuminate whether imaging may identify patients with better or lesser responses to the new therapy. Unfortunately, imaging and therapeutics most often develop in parallel rather than in concert. To the extent that we, as a community, can change this approach would have a potentially

important effect on the use of imaging to help better target therapeutics and improve care for patients with challenging disease states such as cardiac amyloidosis.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. James E. Udelson, Box 70, Division of Cardiology, Tufts Medical Center, 800 Washington Street, Boston, Massachusetts 02111. E-mail: JUdelson@tuftsmedicalcenter.org.

REFERENCES

1. Pitt B, Pfeffer MA, Assmann SF, Boineau R, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; 370:1383-92.
2. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidosis: disease profiles and clinical courses of the 3 main types. *Circulation* 2009;120:1203-12.
3. ClinicalTrials.gov. Safety and efficacy of tafamidis in patients with transthyretin cardiomyopathy (ATTR-ACT). Available at: <http://www.clinicaltrials.gov/show/NCT01994889>. Accessed September 25, 2014.
4. ClinicalTrials.gov. APOLLO: the study of an investigational drug, Patisiran (ALN-TTR02), for the treatment of transthyretin (TTR)-mediated amyloidosis. Available at: <http://www.clinicaltrials.gov/show/NCT01960348>. Accessed September 25, 2014.
5. Lee S-P, Lee ES, Choi H, et al. ^{11}C -Pittsburgh B PET imaging in cardiac amyloidosis. *J Am Coll Cardiol Img* 2015;8:50-9.
6. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol* 2004;55:306-19.
7. Biancalana M, Koide S. Molecular mechanism of thioflavin-T binding to amyloid fibrils. *Biochim Biophys Acta* 2010;1804:1405-12.
8. Antoni G, Lubberink M, Estrada S, et al. In vivo visualization of amyloid deposits in the heart with ^{11}C -PiB and PET. *J Nucl Med* 2013;54:213-20.
9. Chen W, Dilsizian V. Molecular imaging of amyloidosis: will the heart be the next target after the brain? *Curr Cardiol Rep* 2012;14:226-33.
10. Maceira AM, Joshi J, Prasad SK, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation* 2005;111:186-93.

KEY WORDS cardiac amyloidosis, cardiac magnetic resonance, echocardiography, Pittsburgh B compound, positron emission tomography